REMARKS

On page 2 of the Office Action, the Examiner rejects Claims 2-7 and 9-10 under 35 U.S.C. § 112, second paragraph.

Specifically, the Examiner states that Claim 9 is confusing, in that there is no clear indication that the "test compound" and the "antibiotic" are different compounds.

In order to over the Examiner's rejection, Claim 9, step (ii) has been amended to recite "incubating a sample of said phenotypically antibiotic-resistant subpopulation with said test compound, wherein said test compound is different from said antibiotic".

In addition, the Examiner contends that there is no clear nexis between the growth of the "antibiotic-sensitive" bacterial strain to stationary phase, the obtaining of a dormant culture and the treatment with "at least one antibiotic at a concentration and for a sufficient time to kill growing bacteria", i.e., the Examiner contends that not all antibiotics selectively kill growing bacteria only.

Claim 9 relates to an antibiotic which is capable of killing growing bacteria of the same strain as the dormant culture. The growing bacteria of the same strain referred to would be different individual organisms that are not in a dormant state. Thus, Claim 9, step (a) has been amended to more clearly recite "growing an antibiotic-sensitive bacterial strain to a stationary phase to thereby obtain a dormant culture of said antibiotic-sensitive bacterial strain". Claim 9 has also been amended to specify that the growing bacteria are of the same strain and not the same individual organisms.

Furthermore, Claim 9 has been amended to define the "at least one antibiotic" as one which will kill the antibiotic-sensitive bacterial strain, i.e., step (b) of Claim 9 has been amended to recite "treating the resulting dormant culture of said antibiotic-sensitive bacterial strain with an antibiotic which is capable of killing growing bacteria of the same strain at a concentration and for a time sufficient to kill growing bacteria of said strain...".

The Examiner is requested to note that after the dormant bacteria are induced back to the actively growing state, further doses of the antibiotic can be administered by the methods described in the examples. Where the antibiotic is then effective in killing the previously dormant bacteria, the resistance shown during dormancy must have been of the transient, i.e., phenotypic type and not genetic type.

Moreover, the actual concentration of test compound is not an essential feature of the invention. Nonetheless, Claim 9 has been amended to specify that the "concentration" is a "*selected pharmaceutically acceptable concentration*". This should exclude the situation objected to by the Examiner, where any compound can possess anti-bacterial activity at very high concentrations.

The examples provided in the specification clearly disclose adequate methods of killing bacteria to leave only dormant (live) bacteria behind in the test sample (e.g., Example 1). The description states that dormant bacteria *in vivo* can be returned to an actively growing state by, for example, administering steroids to the host animal (page 2, line 37 to page 3, line 3).

The Examiner further contends that there is no claim designated indication regarding the protocol for selecting a phenotypically antibiotic sub-population.

The Examiner is requested to note that there is no special "selection" protocol. In any event, to overcome the Examiner's rejection, Applicants amend the expression "selecting" to "isolating" a phenotypically antibiotic-resistant sub-population from the resulting treated culture.

The Examiner further contends that the resistance of the bacterial strains appears to be to one specific antibiotic, rather than "at least one antibiotic" as recited in Claim 9.

Under U.S. practice, the expression "an antibiotic" is broad enough to include testing more than one antibiotic. Thus, in order to overcome the Examiner's rejection, Applicants simply delete "at least one" from Claim 9, step (b).

The Examiner further contends that it can not be concluded from the process steps that resistance to all antibiotics is implied.

Applicants submit that the above-suggested amendment, i.e., deleting "at least one" overcomes this objection.

The Examiner further contends that the determination of "exhibits any anti-bacterial activity" is uncertain since the concentration of the test compound has not been set forth.

In order to overcome the Examiner's rejection, Applicants amend step (iii) of Claim 9 to recite "assaying whether said test compound exhibits <u>at a selected pharmaceutically acceptable concentration...</u>".

The Examiner further contends that there is no indication of what constitutes the antibacterial activity, i.e., the Examiner asks whether it is slowing of growth for a few minutes, slowing of growth for a few hours, or is it killing.

The Examiner is requested to note that the activity would be killing activity, and that such would be readily understood by one skilled in the art. Thus, to overcome the Examiner's objection, Applicants amend Claim 9 to define the antibacterial activity "as killing of said dormant bacteria".

Moreover, the Examiner states that the step of "assaying" in Claim 9 does not set forth how the antibacterial activity is assayed, i.e., how the assay is done and scored and the concentration of the test compound at which the "any" antibacterial activity has to be exhibited.

In view of the amendments to Claim 9 to recite that the antibacterial activity is killing of said dormant bacteria, and also in view of the deletion of "any", the Examiner's rejection is believed to be met.

Accordingly, Applicants respectfully submit that the claims clearly and definitely recite the invention of interest, and thus request withdrawal of the Examiner's rejection.

On page 3 of the Office Action, the Examiner contends that Claims 2, 5 and 6 fail to provide proper antecedent basis for Claim 9 for "said antibiotic", since the language of Claim 9 is "at least one antibiotic".

In view of the amendments to Claim 9, this rejection has been rendered moot.

Also, on page 3 of the Office Action, the Examiner rejects Claims 3-4 and 9 under 35 U.S.C. § 102(b) as being anticipated by Entenza et al (I) or (II).

Specifically, the Examiner states that Entenza et al (I) and (II) disclose a process for identifying whether a test compound has any antibacterial activity against dormant bacteria, wherein resistant bacteria are produced by treating stationary cultures with at least one antibiotic to select for resistant bacteria.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Initially, Applicants note that Claims 2, 5-7 and 10 have not been included in this rejection.

Entenza et al (II) is directed to investigating the importance of phenotypic tolerance of a single antibiotic (penicillin) *in vivo*, and not the identification of drugs capable of killing dormant bacteria that are already resistant to an antibiotic.

Furthermore, Entenza et al (II) does not disclose all the features of amended Claim 9, as it does not describe a test compound that is distinct from the antibiotic used to produce the phenotypically-resistant culture. Instead, Entenza et al (II) describes the use of both penicillin to produce a phenotypically-resistant culture and as the test compound *in vivo*.

The amendments made to Claim 9 (step ii) clarify that the test compound is different from the antibiotic.

While the Examiner might contend that streptomycin is the antibiotic and penicillin the test compound in Entenza et al (II),

this is clearly not the case, as streptomycin is stated on page 71, left column, middle of fourth paragraph, to only be present in order to prevent contamination during the enrichment cycle, i.e., during growth of the bacteria being studied. Hence, streptomycin used in Entenza et al (II) does not fulfill step (i)(b) of Claim 9, i.e., the streptomycin does not kill growing bacteria of the same strain as the dormant bacteria.

As to Entenza et al (I), this reference is directed to investigating endocarditis due to methicillin-resistant *S. epidermidis* (MRSE).

However, Entenza et al (I) does not disclose all of the feature of amended Claim 9 as it does not describe a dormant culture of antibiotic-resistant bacteria that is sensitive to the same antibiotic while growing.

Entenza et al (I) states on page 102 (right column, last paragraph) that the MRSE bacteria being studied:

> ...contained subpopulations of bacteria able to grow on plates containing 500-1000 mg of methicillin/L.

Hence, the methicillin of Entenza et al (I) does not fulfill step (i)(b) of Claim 9, i.e., the methicillin does not kill growing bacteria of the same strain as the dormant bacteria. Thus, the resistance to methicillin is not limited to dormant bacteria, and does not anticipate the present claims.

Furthermore, the MRSE bacteria studied in Entenza et al (I) are exposed to a test compound while still growing, i.e., they

are not a dormant culture. This is demonstrated on page 101 (left column, last paragraph):

> Serial dilutions of MRSE cultures in the last exponential phase of growth were inoculated onto C agar plates. (Emphasis added)

Additionally, the abstract of Entenza et al (I) states that after 16 hours of logarithmic growth:

> ...growth rate sharply declined. (Emphasis added)

A skilled person would understand "sharply declined" to mean that a decrease in growth had occurred, but that growth was still occurring. This is in contrast to the requirement of the presently claimed invention for the bacteria being studied to be a "dormant culture", i.e., for no growth to be occurring.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Entenza et al (I) and (II). Thus, Applicants request withdrawal of the Examiner's rejection.

In addition, on page 3 of the Office Action, the Examiner rejects Claims 3-4 and 9 under 35 U.S.C. § 102(b) as being anticipated by Boswell et al.

Specifically, the Examiner states that Boswell et al discloses a process for identifying whether a test compound has any antibacterial activity against dormant bacteria, wherein resistant bacteria are produced by treating stationary cultures with at least one antibiotic to select for resistant bacteria.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Initially, Applicants note that Claims 2, 5-7 and 10 have not been included in this rejection.

Boswell et al is directed to investigating a quinupristin/dalfopristin combination drug on *Staphylococcus aureus*, and not identifying drugs capable of killing dormant bacteria that are already resistant to an antibiotic.

Also, Boswell et al does not disclose all of the features of amended Claim 9, as it does not describe a test compound that is distinct from the antibiotic used to produce the phenotypically-resistant culture. Instead, Boswell et al describes the use of a combination of quinupristin/dalfopristin to study the speed at which the combination drug kills *S. aureus* bacteria. In this method, the quinupristin/dalfopristin combination represents both the antibiotic and the test compound.

The amendments to Claim 9 (step ii) clarify that the test compound is different than the antibiotic.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Boswell et al. Thus, Applicants request withdrawal of the Examiner's rejection.

On page 4 of the Office Action, the Examiner rejects Claims 3-4 and 9 under 35 U.S.C. § 102(b) as being anticipated by Tuomanen et al.

Specifically, the Examiner states that Tuomanen et al discloses a process for identifying whether a test compound has any antibacterial against dormant bacteria, wherein resistant bacteria are produced by treating stationary cultures with at least one antibiotic to select for resistant bacteria.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Again, Applicants note that Claims 2, 5-7 and 10 have not been included in this rejection.

Tuomanen et al describes dormancy in the bacteria produced by nutrient starvation, and the subsequent antibacterial activity of a single compound, e.g., Nocardin A, against the nutrient-starved bacteria.

Thus, Tuomanen et al does not describe both steps (a) and (b) of step (i) of Claim 9, i.e., the production of a population of dormant cells which are exposed to both (i) an antibiotic which gives rise to a dormant phenotypically-resistant bacteria, and subsequently (ii) a test compound.

Tuomanen et al states on page 2, in the opening two sentences:

> Phenotypic tolerance is recognized as a general mechanism of survival by which all non-growing bacteria evade killing by antibiotics. Even harsh treatment with detergents fails to kill extensively starved cells leading to the perception that phenotypically tolerant pathogens are extremely difficult, if not impossible, to eradicate.

Tuomanen et al does not disclose all of the steps necessary to perform the method of Claim 9, but instead provides the skilled person with the teaching that killing of phenotypically-resistant bacteria is "extremely difficult", if not impossible.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Tuomanen et al. Thus, Applicants request withdrawal of the Examiner's rejection.

In addition, on page 4 of the Office Action, the Examiner rejects Claims 2-4, 6-7 and 9-10 under 35 U.S.C. § 103 as being unpatentable over Entenza et al (I) or (II) or Boswell et al, or Tuomanen et al in view of Shomura et al and Barth et al.

Specifically, the Examiner states that the primary references (Entenza et al (I) or (II), Boswell et al, and Tuomanen et al) differ from the claimed invention in that *E. coli* resistant to kanamycin and *S. aureus* resistant to ampicillin are not specifically disclosed. However, the Examiner contends that Shomura et al discloses a screening test for antibacterial agents effective against resistant bacteria, wherein kanamycin-resistant *E. coli* are taught, and Barth et al discloses a screening test for antimicrobial agents effective against resistant bacteria, wherein ampicillin-resistant *S. aureus* are disclosed.

Further, the Examiner states that Shomura et al provides guidelines about maximizing the production of the compound of interest, which the Examiner deems to constitute "amplification", as recited in Claim 10.

Hence, the Examiner concludes that it would have been obvious to one skilled in the art to modify the processes of the primary references to use the bacterial strains and antibiotics of the secondary references, to achieve the invention.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

As discussed above, neither Entenza et al (I) and (II), nor Boswell et al, or Tuomanen et al teach or suggest the present invention. Further, for the following reasons, it is clear that

Shomura et al and Barth et al do not provide the deficiencies that exist therein.

Shomura et al is directed to the antibacterial compounds SF-767-A and SF-767-L. These compounds are capable of killing growing bacteria, including those resistant to other antibiotics. However, Shomura et al only discloses the use of these compounds as growth-inhibitory compounds (see column 1, second paragraph). Therefore, these compounds are not described in Shomura et al as having potential uses in killing dormant bacteria. As such, one of ordinary skill in the art would not seek to use the compounds of Shomura et al with the teaching of Entenza et al (I), Entenza et al (II), Boswell et al or Tuomanen et al to achieve the present invention.

With regards to the alleged disclosure by Shomura et al of amplification of compounds identified as killing dormant bacteria, even in light of the above arguments, it would be clearly understood that the amplification described by Shomura et al in Examples 1 and 2 occurs before exposure to the bacteria. In the present invention, amplification of the test compound occurs after the compound has been identified as killing the dormant bacteria.

In order to clarify this difference, Claim 10 has been amended to read:

> ...further comprising the step of amplifying said test compound after said test compound is identified by step (iii).

Support of this amendment can be found in the paragraph spanning pages 8 and 9 of the present specification.

As to Barth et al, this reference teaches penicillanic acid 1,1 dioxides as being β-lactamase inhibitors. There is no disclosure in Barth et al of dormant bacteria nor compounds which can be used to kill dormant bacteria, as claimed in the present invention. As is the case with Shomura et al, a person of ordinary skill in the art would not seek to use the compounds of Barth et al with the teaching of Entenza et al (I), Entenza et al (II), Boswell et al or Tuomanen et al to achieve the present invention.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Entenza et al (I) or (II), Boswell et al, and Tuomanen et al alone, or when combined with Shomura et al and Barth et al. Thus, Applicants request withdrawal of the Examiner's rejection.

Finally, on page 5 of the Office Action, the Examiner rejects Claim 5 under 35 U.S.C. § 103 as being unpatentable over Entenza et al (1996) or (1994) or Boswell et al or Tuomanen et al taken with Shomura et al and Barth et al, and taken further in view of Murray et al and *The Merck Index*.

The Examiner notes that Claim 5 differs from the cited references in that rifampicin-resistant *M. tuberculosis* is not disclosed in the cited references. However, the Examiner states that Murray et al demonstrates that resistance to rifampicin in *M. tuberculosis* is recognized in the art, and *The Merck Index* disclose that rifampin and rifampicin are one and the same. Hence, the Examiner concludes that it would have been obvious to one skilled in the art to modify the processes of the primary references by using the antibiotic and bacterial strains of

Murray et al and *The Merck Index* to achieve the present invention.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

As discussed above, neither Entenza et al (I) and (II), nor Boswell et al, or Tuomanen et al even when combined with Shomura et al and Barth et al teach or suggest the present invention. Further, for the following reasons, it is clear that Murray et al and *The Merck Index* do not provide the deficiencies that exists therein.

Murray et al teaches that rifampicin resistance is due to a mutation in the rpoB gene (page 428, left column, last paragraph). Clearly this rifampicin resistance is genetic, and does not constitute the phenotypic resistance required by Claim 9.

As to *The Merck Index*, this reference only demonstrates that Rifampin and rifampicin are the same compound.

Therefore, a skilled person would not seek to combine Murray et al with any of Entenza et al (I), Entenza et al (II), Boswell et al or Tuomanen et al in combination with Shomura et al or Barth et al, because the teaching of Murray et al is from a different technical field (genetic as opposed to phenotypic-resistance).

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Entenza et al (I) or (II), Boswell et al, and Tuomanen et al alone, or when combined with Shomura et al, Barth et al,

Murray et al and *The Merck Index*. Thus, Applicants request withdrawal of the Examiner's rejection.

In view of the amendments to the claims and the arguments set forth above, reexamination, reconsideration, and allowance are requested.

The Examiner is invited to contact the undersigned at his Washington telephone number on any questions which might arise.

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